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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,128	02/20/2004	James McSwiggen	MBHB04-105 (400.146)	2611

20306 7590 04/03/2006

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/783,128	MCSWIGGEN, JAMES	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,10-21,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,10-21,30 and 31* is/are rejected.

7)☒ Claim(s) *30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/11/05, 12/23/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 1/10/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 08/10/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 1/10/2006, claims 1, 3, 10-21 and 30-31 are pending in the application. Applicant has canceled claims 2, 4-9 and 22-29.

New Rejections/Objections

Claim Objections

Claim 30 is objected to because of the following informalities: Claim 30 depends from a canceled claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 10-14, 19-21 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al. (recited on PTO form 892 filed 08/10/2005) in view of Agrawal et al. (see PTO form 1449, page 7 filed 8/10/2005) in further view of Bennett et al. (U.S. Patent No. 5,998,148).

The instant claims are drawn to a double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human HD nucleotide sequence, wherein each strand is 18 to 27 nucleotides in length, wherein the double stranded nucleic acid molecule comprises at least two different chemically modified nucleotides, wherein the double stranded nucleic acid molecule comprises one or more ribonucleotides, wherein the sense strand is connected to the antisense strand via a linker molecule, wherein the linker molecule is a polynucleotide or a non-nucleotide linker, wherein one or more pyrimidine nucleotides in the sense strand are 2'-O-methyl or 2'-O-deoxy, wherein one or more purine nucleotides are 2'-deoxy or 2'-O-methyl, wherein the antisense strand comprising a terminal phosphorothioate internucleotide linkage and further drawn to a pharmaceutical composition comprising said double stranded nucleic acid.

Hayden et al. teach an antisense compound targeted to a HD gene (see paragraph 0082). Hayden et al. further teach the antisense compound can be between 15-30 nucleotides in length and the antisense compound can be modified to increase the biological stability (see paragraph 0087). Hayden et al. do not teach a double-

stranded nucleic acid molecule targeted to a HD gene and further do not teach the nucleotides of the double-strands can be modified.

Agrawal et al. teach a self-stabilized antisense molecule comprising a sense strand and an antisense strand (see Figure 5). Agrawal et al. teach the self-stabilized regions can comprise 50 nucleotides or less i.e. either strand comprises 25 nucleotides or less (see page 15, lines 5-30). Agrawal et al. teach the self-stabilized double stranded molecule can comprise modified ribonucleotides, such as 2'-O-methyl and further the self stabilized region may be connected with a nucleotide (see page 15, lines 8-20) or non-nucleotide linkers (see page 15, lines 31-36). Agrawal et al. teach

Bennett et al. teach common chemical modifications to antisense molecules wherein the nucleic acid comprises at least two different chemically modified nucleotides, such as a sugar or nucleobase modification (see columns 7-9).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate self-stabilizing regions, as taught by Agrawal et al., into the antisense compound targeted to a nucleic acid encoding HD as taught by Hayden et al. Further it would have been obvious for one of ordinary skill in the art to make a self-stabilized nucleic acid molecules with two different chemical modifications, as taught by Bennett et al.

One would have been motivated to make a self –stabilized nucleic acid because Agrawal et al. teach self-stabilized nucleic acids are more resistant to nucleolytic degradation (see page 8, lines 1-20). Agrawal et al. further teach the self-stabilized nucleic acids can be made hyperstabilized by incorporation of modified ribonucleotides,

such as 2'-O-methyl and addition of internucleotide linkages (see page 17, lines 26-35), modifications that are routine to one of skill in the art. Further, Bennett et al. provide motivation to incorporate different types of nucleotide modifications such as sugar and substituted purine and pyrimidine base modifications and particularly base modifications are useful in increasing the nucleic acid stability, especially when combined with 2'-O-methylethyl sugar modifications (see column 8, lines 45-58).

Finally, one would have a reasonable expectation of success because Hayden et al. teach antisense molecules can be targeted to a HD gene and regulate gene expression and Agrawal et al. demonstrates increased stability of self-stabilizing antisense molecule and further Bennett et al. teach that chemically modification nucleotides are useful and add stability and specificity to oligonucleotides were known in the art at the time of the invention was made.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 3, 10-21 and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al. (recited on PTO form 892 filed 08/10/2005), Hammond et al. (recited on PTO form 892 filed 08/10/2005), Tuschl et al. (WO 02/44321), Parrish et al. (recited on PTO form 892 filed 08/10/2005) and in further view of Matulic-Adamic (recited on PTO form 892 filed 08/10/2005), Thomson et al. (Nucleic Acids Research 1993) and Schmidt et al. (recited on PTO form 892 filed 08/10/2005).

The instant claims are drawn to a double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human HD nucleotide sequence, wherein each strand is 18 to 27 nucleotides in length, wherein the double stranded nucleic acid molecule comprises at least two different chemically modified nucleotides, wherein the double stranded nucleic acid molecule comprises one or more ribonucleotides, wherein the sense strand is connected to the antisense strand via a linker molecule, wherein the linker molecule is a polynucleotide or a non-nucleotide linker, wherein one or more pyrimidine nucleotides in the sense strand are 2'-O-methyl or 2'-O-deoxy-2'-fluoro, wherein one or more purine nucleotides are 2'-deoxy or 2'-O-methyl, wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the terminal cap moiety is an inverted deoxy abasic moiety, wherein the antisense strand comprising a terminal phosphorothioate internucleotide linkage, wherein a non-nucleotide comprises an abasic moiety, the 5' end includes a terminal 5'-phosphate and further drawn to a pharmaceutical composition comprising said double stranded nucleic acid.

Hayden et al. teach an antisense compound targeted to a HD gene (see paragraph 0082). Hayden et al. further teach the antisense compound can be between 15-30 nucleotides in length and the antisense compound can be modified to increase the biological stability (see paragraph 0087). Hayden et al. do not teach a double-stranded nucleic acid molecule targeted to a HD gene and further do not teach the nucleotides of the double-strands can be modified.

Hammond et al. teach two methods for silencing specific genes: antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "...questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach " "...dsRNAs have been shown to inhibit gene expression in a sequence-specific manner" and further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression." Hammond et al. do not teach double-stranded nucleic acid comprising two different chemically modified nucleotides, comprising 2'-O-methyl, 2'-deoxy or 2'-deoxy-2'-fluoro, or comprising two separate strands connected via a linker molecule, or a double stranded nucleic acid molecule wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the terminal cap moiety is an inverted deoxy abasic moiety, wherein the antisense strand comprising a terminal phosphorothioate internucleotide linkage, wherein a non-nucleotide comprises an abasic moiety, the 5' end includes a terminal 5'-phosphate and or a pharmaceutical composition comprising said double stranded nucleic acid.

Tuschl et al. teach siRNA molecules which are 21 nucleotides in length and wherein each separate strand comprises at least 19 nucleotides complementary to the nucleotides of the other strand (Figure 14) and further teach 2'-deoxy thymidine, an abasic moiety, can be substituted for uridine at the 3' ends, i.e. a terminal cap. Tuschl et al. further teach substitutions on either strand by 2'deoxy residues or 2'-O-methyl residues are well tolerated (see Figure 14). Tuschl et al. teach the siRNA can comprise

at least two different chemically modified nucleotides wherein the siRNA comprises one or more modified sugar or backbone nucleotides as listed (see page 5, lines 5-31) and the modifications can be combined i.e. the siRNA can comprises both a modified sugar and a modified backbone nucleotide which are different (see page 6, lines 1-6). Tuschl et al. teach a 5'-phosphate on the antisense strand is required for siRNA function (see page 4, lines 12-20) and teach pharmaceutical compositions comprising double stranded nucleic acids and an acceptable carrier (see page 9, lines 17-25) and teach the siRNA can mediate degradation in mammalian cells (see Example 2).

Parrish et al. teach a siRNA with an antisense or sense region comprising 2'-deoxy-2'-fluoro pyrimidine nucleotides (see Figure 5) and further teach this siRNA can mediate degradation of cellular RNA (see abstract page 1082).

Matulic-Adamic et al. teach double stranded structures comprising abasic terminal cap moieties that provide resistance to degradation (see column 2, lines 44-55 and column 3 lines 1-68). Matulic-Adamic et al. further teach a double stranded structure comprising separate sense and antisense strands and further wherein this structure comprises a connecting loop comprising a linker or non-nucleotide linker (see Figure 3). Thomson et al. teach a similar structure to Matulic-Adamic wherein the double stranded structure comprising a linker (see Figure 1). Thomson et al. teach linkers increase efficiency of production and further enhance the molecules stability (see page 5602, second column). Schmidt et al. teach a hairpin RNA comprising a sense and an antisense region connected via a linker that is a polynucleotide or non-

polynucleotide (see Figure 3). Schmidt et al. teach the linkers increase hairpin RNA cleavage efficiencies (see page 575).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a double stranded nucleic acid molecule, as taught by Hammond et al., Tuschl et al. and Parrish et al. to target a gene encoding HD, as taught by Hayden et al. Further it would have been obvious for one of ordinary skill in the art to make a double stranded nucleic acid molecules with chemical modifications, as taught by Tuschl et al., Parrish et al. and Matulic-Adamic.

One would have been motivated to use a double stranded nucleic acid targeted to a HD gene and inhibit gene expression because Hayden et al. teach HD proteins are involved in neurodegenerative diseases and inhibition of HD expression controls cell survival (see paragraph 0007). One would have been motivated to use a double stranded nucleic acid targeted to HD instead of an antisense because it was well known at the time the invention was made that dsRNA molecules are efficient molecules to target and decrease expression of a target gene and because Hammond et al. teach using dsRNA to inhibit gene expression is more sequence specific than using antisense methodologies and RNAi using dsRNA is a more potent method requiring only a few molecules of dsRNA per cell. Further, Tuschl et al. and Parrish et al. provide motivation to incorporate 2'-O-methyl, 2'-deoxy or 2'-deoxy-2'-fluoro chemical modifications because the modifications are important for mediating RNA interference. Further, Tuschl et al. provide motivation by demonstrating siRNA decreased gene inhibition in mammalian cells. Additionally, Tuschl et al., Matulic-Adamic et al., Thomson et al. and

Schmidt et al. provide motivation to make a dsRNA with terminal cap moieties to provide resistance and degradation and further provide motivation to connect sense and antisense strands via a linker to increase efficiency of production.

Applicant argues Matulic-Adamic et al. is not pertinent to the problem addressed by the presently claimed compounds because Matulic-Adamic et al. is drawn to a ribozyme which is unrelated to RNAi. The amended claims are broadly drawn to any double stranded nucleic acid and do not excluded ribozymes. Nevertheless, Matulic-Adamic et al. is relied upon to teach obvious chemical modifications to any nucleic acid molecule, such as a dsRNA, for the purpose of increasing nuclease resistance, stability and target specificity: modifications that would be obvious to one of skill in the art to incorporate into a nucleic acid molecule used to target a specific gene for inhibition of expression.

Finally, one would have a reasonable expectation of success because Hayden et al. teach antisense molecules can be targeted to a HD gene and regulate gene expression, Hammond et al. teach that of the two methods used for silencing gene function, RNAi using dsRNA is more potent and sequence specific than antisense and finally Tuschl et al. and Parrish et al. teach designing double stranded nucleic acids with chemical modifications that mediate RNA interference. Further, one would have a reasonable expectation of success because chemical modifications of an oligonucleotide, adding stability and specificity to oligonucleotides were known in the art at the time of the invention was made. Additionally, one would expect such

modifications would benefit siRNAs because such modifications had been shown to benefit antisense or ribozymes.

Applicant argues, in the Remarks/Arguments filed 01/10/2006, the cited references, namely Hayden et al., Hammond et al., Parrish et al., do not provide a reasonable expectation of success of making a double stranded nucleic acid molecule comprising a sense strand and an antisense strand targeted to an gene encoding HD.

To the contrary, one of skill in the would have had a reasonable expectation of success because it was well known to one of skill in the art that not only did siRNA technology exist, as stated by Applicant on page 19 of remarks, but that suppression of gene activity was achieved in mammalian cells using siRNA (see Tuschl et al. Example 2). Therefore, one would have had a reasonable expectation of success at making a dsRNA targeted to a gene encoding HD and success at incorporating chemical modifications because they had been shown to benefit similar inhibitory nucleic acid molecules.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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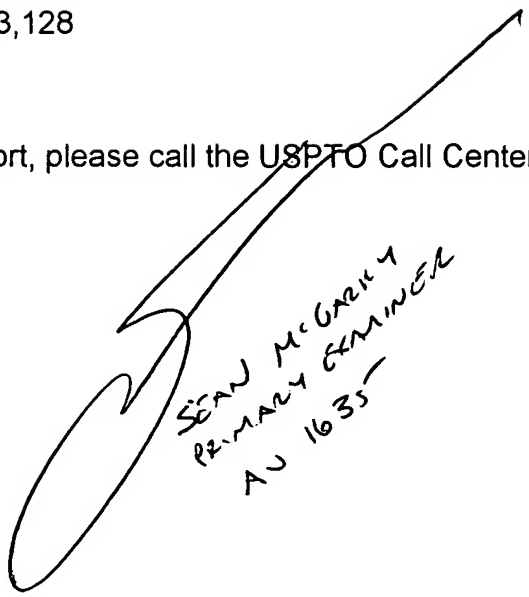

Kimberly Chong
Examiner
Art Unit 1635